Ethical Issues in the Use of Stored Samples

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A Note about Terminology

“samples”

“tissues”

“specimens”

“human biological materials”

Where are stored samples?
(n>282 mil.)

- Individual laboratories
- Multi-center trials
- Pathology departments
- Newborn screening programs
- “Biobanks”
- Military DNA collections
- Forensic collections

Definition of Human Subject

(f) A living individual from whom an investigator . . . conducting research obtains:

(1) data through intervention or interaction with the individual

45 CFR 46.102


S98-5560
S199-3126
S95-0322
S95-271
S99-3093
S93-1539
S95-0025
S97-0479 B
1-86-9020
S199-3700
1-85-16625
1582-7483
1583-4617
98-1281-2
98-1281-1
98-513

Definition of Human Subject

(f) A living individual from whom an investigator . . . conducting research obtains:

(1) data through intervention or interaction with the individual

(2) identifiable private information

45 CFR 46.102

What is *not* research with human subjects?

Collection and study of:

- Samples from deceased individuals
- Samples taken for diagnostic purposes only
- Specimens or data that are available from commercial or public repositories or registries
- Established cell lines that are publicly available to qualified scientific investigators
- Self-sustaining, cell-free derivative preparations including viral isolates or cloned DNA

From OHSR Information Sheet #14

Case 1
HCV “Look-Back” Study

- Problem
  - Need for research on long-term outcomes for young, healthy persons with hepatitis C infection
- Potential Solutions
  - Prospective studies
  - Retrospective cohort study using stored samples

L Seeff *et al.*, 2000, *Ann. Int. Med.*

HCV Study Procedures

- Serum specimens (n=8568) collected between 1948-1954 from military recruits for group A strep and acute rheumatic fever
  - Tested for presence of HCV antibodies
  - Names and military service numbers matched to SS#s + demographics
  - Morbidity and mortality data collected from VA and HCFA records

HCV Findings

- Historical significance
  - HCV in US prior to 1968
- Healthy HCV+ individuals may be at less risk for progressive liver disease than is currently thought
  - 2/17 (12%) HCV+ and 205/8551 (2%) HCV-individuals had developed liver disease

HCV Study: Questions

- When should subjects be asked to “re-consent” prior to new research on samples?
  - Military vs. other contexts
- When is it appropriate to inform individuals regarding + results?
  - Potential benefits vs. risks to subjects
  - Additional scientific knowledge to be gained
  - 7/10 HCV+ individuals still living were recontacted

Case 2
BRCA1/2 and Tamoxifen

- BCPT (n>13,000)→ tamoxifen significantly reduced incidence of invasive breast cancer in high-risk women
  - Conducted 1992-1998, before BRCA1/2 cloned
  - Study did not show *who* would benefit most
- Investigators wanted to go back to DNA samples to test for BRCA1/2 mutations

Fisher *et al.* 1998, *J Natl Cancer Inst*; MC King *et al*., 2001, *JAMA*

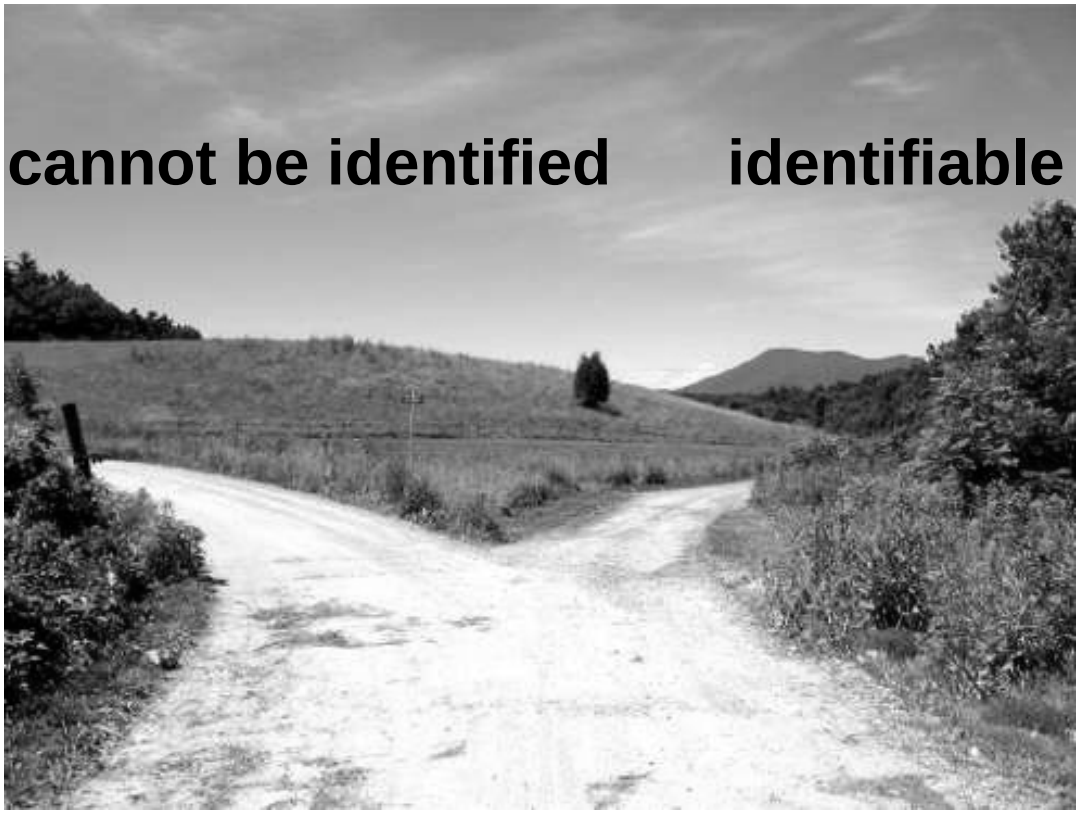
BRCA1/2 Testing: Consent

- Women had not given explicit consent for BRCA1/2 genetic testing
  - General consent for future genetic research
- Subjects were informed about the new study
  - Given opportunity to “opt out” and withdraw DNA sample
- Samples were “anonymized”
  - No genetic results given

Concerns: Use of Stored Samples

- Research design
  - Collection of new samples vs. use of existing samples
  - Plans for linking samples to medical records, identifiable information
  - Use/disclosure of research results
- Informed consent
  - Adequate disclosure
    - Prospective
    - Existing, stored samples

Classification of Samples



45 CFR 46

Classification of Samples

- “Cannot be identified”
  - No “human subject” if truly not identified
  - Question of how much clinical and demographic data can be retained
- “Identifiable”
  - Directly (name/ID)
  - Coded/linkable
    - Depends on who has access to identifiers

Confused?

Anonymous
Anonymised
Anonymously coded
Unidentified
De-identified
De-linked
Permanently de-linked
Irreversiblement anonymisé
Not traceable
Irretrievably unlinked to an identifiable person (UNESCO)
Completely anonymised
Unlinked anonymised
Traceable
Réversiblement anonymisé
Coded

Identifiably linked
Pseudonomised
Unlinked
Unlinked to an identifiable person (UNESCO)
Encoded
Encrypted
Identified (NBAC)
Nominative
Directly identified (Clayton et al 1995)
Fully identifiable
Confidential (NHS Confidentiality Strategy)
Linked to an identifiable person (UNESCO)
Identifiable
Personal data

Historical Interpretation:

not identifiable = anonymous

- “Even if the researcher cannot identify the source of tissue, the samples are not anonymous if some other individual or institution has this ability.”

Clayton et al, *JAMA,* 1995

Current Interpretation:

not identifiable = not readily ascertainable

- "OHRP does not consider research involving only coded private information or specimens to involve human subjects . . . if the following conditions are both met:
  - (1) the private information or specimens were not collected specifically for the proposed research . . . and
  - (2) the investigators cannot readily ascertain the identity of the individual(s)"

OHRP Guidance, 8/10/04

NIH Policy: IRB Review

- Use of stored identified or coded specimens or data, when IRP researcher can identify sources
  - Prospective and ongoing IRB review required
- Use of stored coded samples when IRP researchers cannot identify subjects
  - May not require NIH IRB review
  - Contact OHSR for guidance
- Use of stored, unlinked or unidentified samples
  - May be exempt from the need for prospective IRB review
  - Requests must be submitted in writing to OHSR

OHSR Information Sheet #14

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OHSR Information Sheet #14

Risks of Using Identifiable Samples

Disclosure

- To third parties
  - Potential for breach of privacy and confidentiality
- To patients/subjects
  - Privacy intrusion from undesired contact
  - Harm from disclosure of results

Research Design Measures to Reduce These Risks

- Maximize confidentiality
  - The “least necessary” or “least identifiable” dataset
  - Use of intermediary to hold link between code and identifiers
  - Obtaining maximal legal and practical protections
    - e.g., data placed on computers not linked to the Internet
- Develop approach for re-contacting subjects
  - Clinical relevance or value
  - Adequate counseling

Societal/Cultural Aspects

- Risks to communities
- Taboos
- Public trust in research

What role does informed consent play?

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Late at night, and without permission, Reuben would often enter the nursery and conduct experiments in static electricity.

Informed Consent for Research on Stored Samples

- If/when?
  - For prospective collection
  - Maybe for existing samples, depending on:
    - Identifiability
    - Adequacy of prior consent
    - Setting in which collected (research vs. clinical)
- How?
  - Extent of detail
  - Frequency

Informed Consent Guidance

- “Research conducted with *unidentified samples* is not human subjects research and is not regulated by the Common Rule.”
- “Research using *coded or identified samples* requires the consent of the source, unless the criteria for a consent waiver have been satisfied.”

NBAC (1999)

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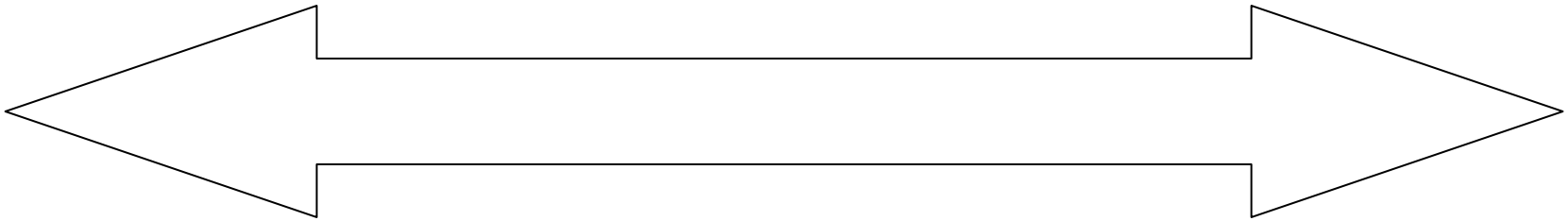
NBAC (1999)

Waiver of Informed Consent for Use of Stored Samples
(see 45 CFR 46.116)

- Protocol must pose minimal risk
  - Determination of whether it might be desirable to communicate directly with patients
    - If yes, then > minimal risk, and consent should be obtained
- Cannot adversely affect rights and welfare
- Impracticability of obtaining consent
  - From some or all participants

Informed Consent

- What information is necessary to disclose for informed consent to be “valid”?



Any genetic research

Specific disease

Particular gene

Explicit methodology

Individual investigator

Distinct time

Unspecified Consent Forms

"I consent to the donation of my tissues for research and education. If you wish to decline donation, indicate with your initials here_____."

CAP consensus statement (1999)

Explicit Consent

Recommendation 9:

> . . . to provide potential subjects with a sufficient number of options to help them understand clearly the nature of the decision they are about to make.

NBAC Report (1999)

Explicit Consent
Possible Options (“Menu Approach”)

- Only unidentified or unlinked use
- Use in one study only, no further contact
- Use in one study, with possible further contact
- Use in any related study, with possible further contact
- Use in any kind of study

NBAC Report (1999)

A Role for Empirical Data

- Consent form content
- Subject attitudes and informational needs
- Subject consent “behaviors”

Consent Form Content @ NIH

(n=230)

- Options in consent forms 20%
  - Any future research
  - Unrelated diseases
  - Specific confidentiality protections
  - Share with other researchers
  - Additional consent
- Offer of additional consent 42%
  - Any future research
  - Unrelated diseases
  - Additional risk
  - Specific confidentiality protections
  - Share with other researchers

Hull *et al*., *IRB,* 2004

Subject Attitudes: Need for Informed Consent

Proportion of patients who would require informed consent for research with tissue samples (n=504)

	Anonymous	Identifiable
Clinically-derived	27%	66%
Research-derived	12%	29%

Wendler and Emanuel, *Arch Intern Med* 2002

Arch Intern Med

Subject Attitudes: Future Use of Stored Samples

(n=1193)

Okay to study different diseases	79%
Willing to sign one-time release	73%
Okay for different researchers to use sample to study original disease	61%

Hull et al., in process

Subject Attitudes: Willingness to Give Blood to Genetics Researcher

Very Willing	58%
Moderately Willing	26%
Somewhat Hesitant	11%
Very Hesitant	1%
Unwilling	3%

(N=1193)

Sobolski *et al.* (2006)

Subject Behaviors: The NHANES Experience

- National survey that collects specimens from representative sample of US population
- Of people surveyed in 1999-2000, 84-85% consented to collection of DNA specimen
  - Females and black participants least likely to consent (73-84%, depending on year)

McQuillan *et al.*, 2003, *Genet Med*

Biobanks vs. “Traditional” Research with Samples

- Individual researcher/ team
- One set of defined studies
- Future uses not anticipated
- One study/one consent

- Broker/intermediary supplies samples
- Many studies possible
- Future uses anticipated
- More general (“blanket”) consent?

Current Issues: Biobanks

- Acceptability of “blanket” consent approaches
- Provision of results
- Enrollment of minors
  - Risks
  - Permission/assent and re-consent
- Ownership/commercial aspects
  - Profit/benefit sharing